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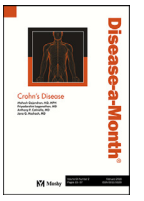

Myasthenia gravis: Mechanisms, clinical syndromes, and diagnosis

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A B S T R A C T

Myasthenia gravis (MG) is an autoimmune neuromuscular disorder characterized by muscle weakness and fatiguability. The pathogenesis of MG is mediated in most cases by autoantibodies directed against the nicotinic acetylcholine receptor at the neuromuscular junction, although less commonly autoantibodies may target muscle-specific kinase (MuSK) or low-density lipoprotein receptor-related protein 4 (LRP4). These autoantibodies disrupt cholinergic transmission at the neuromuscular junction through several mechanisms, including direct functional blocking, downregulation, destruction, or disruption of receptor clustering in the postsynaptic membrane. MG is characterized by fatigable muscle weakness in the ocular, bulbar, respiratory or limb muscles. Clinical manifestations can vary significantly among individuals depending on the type of autoantibody or presence of thymoma. Due to the variable presentation of symptoms, diagnosing MG can be challenging. A comprehensive approach that combines clinical assessment, serological testing, electrophysiological studies, and imaging is essential for accurate diagnosis.

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Introduction

Myasthenia gravis (MG) is an acquired and chronic autoimmune neuromuscular disorder characterized by weakness and fatiguability of voluntary muscles. MG is a relatively rare disorder, with an estimated incidence ranging from 4.1 to 30 cases per million person-years.[1] The prevalence rate is estimated to be around 150 to 200 cases per million people in the general population, although these figures can vary by geographic region and population demographics.[1] The incidence of MG has a bimodal distribution with increased incidence in women under 40 and men over 60 but can affect individuals of any age. MG is a pathologically and phenotypically heterogenous disorder.[2] MG presents with fluctuating muscle weakness that can significantly impact the patients' quality of life.[3] Understanding the underlying pathophysiologic mechanisms, clinical manifestations, diagnostic approaches, and management strategies for MG is crucial for providing effective patient care.

Pathophysiological mechanisms

Role of autoantibodies

The majority of patients with MG (approximately 80 %) have immunoglobulin (Ig)G1 and IgG3 antibodies directed against nicotinic acetylcholine receptors (AChRs) at the neuromuscular junction.[1,2] These antibodies impede cholinergic neuromus-

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cular transmission through several mechanisms. Firstly, there is direct inhibition of acetylcholine binding to the AChR that prevents effective neuromuscular transmission.[4] Moreover, autoantibody binding can also trigger internalization of AChRs, further decreasing the receptor density at the neuromuscular junction.[5] Finally, there is activation of the complement cascade which leads to the destruction of AChRs and the surrounding postsynaptic membrane.[2] These mechanisms ultimately result in a reduced number of functional receptors available for acetylcholine binding at the neuromuscular junction.[6]

In a subset of MG patients (about 5–10 %), the immune response targets muscle-specific kinase (MuSK) or related proteins such as agrin and low-density lipoprotein receptor-related protein 4 (LRP4) .[2] MuSK is a protein that is vital for clustering and aggregation of AChRs at the neuromuscular junction. Antibodies against MuSK are predominantly IgG4 and interfere with AChR clustering, thus leading to a reduction in functional AChRs at the neuromuscular junction.[1,2] The binding of MuSK antibodies can also disrupt downstream signaling pathways necessary for neuromuscular junction maintenance and adaptation, thereby further impairing synaptic transmission.[7,8] IgG4 class autoantibodies can activate complement only at high antigen and antibody concentrations, and only weakly bind Fc-receptors expressed on immune cells instead exerting their pathogenicity via interfering with the interaction between their targets and binding partners (for example between MuSK and LRP4) .[9,10] A notable difference between AChR and MuSK-MG is involvement of the thymus which is not prominent in MuSK-MG. In MuSK-MG, treatment options such as intravenous immunoglobulin (IVIG) are usually less effective with the need for prolonged and high doses of steroids. Moreover, clinical response may require use of other modalities, such as plasmapheresis and anti CD20 therapy with rituximab.[10]

Thymic abnormalities

The thymus gland has a critical role in the development and regulation of the immune system, particularly in T-cell maturation. Thymic abnormalities are commonly observed in MG patients. Many individuals with MG exhibit thymic hyperplasia, an enlargement of the thymus gland due to increased immune activity. This hyperplasia is believed to promote the production of autoantibodies against AChRs and MuSK.[1,2] Thymomas are tumors of the thymus that can occur in MG patients, often leading to more severe forms of the disease. About 50 % of patients with a thymoma will develop MG and 10 %–20 % of MG patients are found to have thymomas.[11] The presence of thymoma is associated with distinct clinical features and a more aggressive disease course.[12] It is hypothesized that thymomas hold epitopes that can cross-react with certain skeletal muscle proteins such as ryanodine receptor (RyR), titin, and AChR. Therefore, in addition to autoantibodies against AChR, the majority of paraneoplastic thymoma-associated MG cases also have striational antibodies against intracellular proteins such as RyR and titin. In many cases of thymoma thymectomy is curative although radiation therapy and chemotherapy may be required.[13,14]

Complement activation

The activation of the complement system plays a significant role in the pathophysiology of MG. The binding of autoantibodies to AChRs leads to activation of the complement cascade. This results in the formation of the membrane attack complex (MAC), which can induce lysis of the postsynaptic membrane at the neuromuscular junction and thus exacerbates the receptor loss.[6] Complement activation also leads to the recruitment of inflammatory cells, which may further damage the neuromuscular junction and contribute to muscle weakness.[6,15]

Role of T-Cells

T-lymphocytes, particularly CD4+ *T*-helper cells, are crucial in the pathogenesis of MG. These cells help orchestrate the autoimmune response and are involved in the production of autoantibodies. T-helper cells interact with B-cells, promoting their maturation and differentiation into antibody-producing plasma cells. This interaction is essential for the sustained production of AChR and MuSK antibodies.[1,2] Activated T-cells also secrete various cytokines that perpetuate inflammation and autoimmunity, further disrupting normal neuromuscular transmission.[16]

Genetic factors

While the vast majority of MG cases are considered autoimmune, genetic predispositions also play a role. Specific HLA (human leukocyte antigen) types, such as HLA-DR3, have been associated with an increased risk of developing MG.[1,17] These genetic factors may influence the immune response, making individuals more susceptible to autoimmunity.

Clinical syndromes

The clinical presentation of MG is diverse and can be classified into various syndromes based on symptomatology, severity, progression, age, type of antibody, and thymoma status. While fatigable muscle weakness that worsens with activity and improves with rest is the hallmark of the disease, its clinical manifestations can vary significantly among individuals. Understanding these clinical syndromes is crucial for accurate diagnosis and effective management.

Ocular myasthenia gravis

Ocular myasthenia gravis (OMG) is the most common initial presentation of MG with the primary symptoms including fluctuating ptosis and diplopia. Most MG patients with ocular symptoms at onset will eventually progress to a generalized MG disease state, usually within two years of onset. Therefore, ocular MG is defined by isolated ocular involvement for a period of at least 2 years.

Generalized myasthenia gravis

Generalized myasthenia gravis is characterized by more diffuse muscle involvement in addition to ocular involvement. Proximal muscles are typically affected more than distal muscles, with patients reporting difficulties with trouble lifting objects, climbing stairs, or raising their arms. Bulbar muscle weakness manifests as dysphagia and dysarthria. Patients are also at an increased risk of developing aspiration pneumonia due to weakening of pharyngeal and laryngeal muscles. Generalized MG can be further classified based on the severity of symptoms using the Myasthenia Gravis Foundation of America (MGFA): ocular-only (I), mild (II), moderate (III), severe (IV) and intubation (V), with additional subclassification related to axial/extremity (a) or bulbar (b) predominance.[18] In the most severe cases there can be respiratory failure due to the involvement of respiratory muscles such as during a myasthenic crisis. Myasthenic crisis is a medical emergency characterized by an exacerbation of muscle weakness and the potential for respiratory compromise.[17,19]

Myasthenic crisis

A myasthenic crisis is a severe exacerbation of MG that requires immediate medical attention. It is characterized by rapidly progressive and severe muscle weakness with impending respiratory failure. Common triggers include infections, surgery, certain medications (such as muscle relaxants, certain antibiotics), or emotional stress.

Several drugs are known to worsen MG by impairing neuromuscular transmission, and their use should be carefully monitored or avoided in affected individuals.[20] Common offending agents include certain antibiotics such as aminoglycosides (e.g., gentamicin), fluoroquinolones (e.g., ciprofloxacin), and macrolides (e.g., azithromycin). Other culprits include beta-blockers, calcium channel blockers, magnesium sulfate, and some anesthetics and muscle relaxants. Additionally, drugs like penicillamine and interferon-alpha have also been associated with triggering or unmasking MG symptoms. Clinicians must therefore do a careful risk-benefit assessment before prescribing these agents and consider alternatives whenever possible.

Immune checkpoint inhibitors, such as nivolumab and pembrolizumab, are immunotherapy drugs used to treat various cancers by enhancing T-cell activity against tumors. However, they can also trigger immune-related adverse events, including the development or exacerbation of MG.[20,21] This immune activation may lead to the production of autoantibodies targeting the neuromuscular junction, resulting in muscle weakness, fatigue, and in severe cases, respiratory failure. Checkpoint inhibitor-induced MG often presents rapidly and may be more severe than idiopathic MG. Management typically involves discontinuation of immunotherapy, high-dose corticosteroids, and immunosuppressive therapies such as IVIG or plasmapheresis. Early recognition and prompt treatment are crucial due to the potentially life-threatening nature of this complication.

Management of a myasthenic crisis often requires emergent hospitalization, respiratory support, and aggressive treatment with plasmapheresis or IVIG.[17,22] Pyridostigmine may be held initially to reduce airway secretions but should be restarted as the patient is approaching extubation.

Thymoma-Associated myasthenia gravis

Approximately 10–20 % of MG patients have thymomas. The presence of a thymoma is associated with a more severe form of MG with more pronounced muscle weakness and a higher incidence of respiratory issues.[24] Thymectomy is often recommended for patients with thymoma and is associated with improvements in symptoms and long-term outcomes.[25]

MG variants

Clinical variants of MG may also be categorized based on autoantibody profiles or specific clinical features. MuSK-positive MG typically presents with more bulbar symptoms and less ocular involvement compared to AChR-positive MG.[1,2] In contrast to AChR antibodies whose titers do not significantly correlate with clinical MG severity, MuSK antibody titers do tend to correlate directly with disease severity. Some patients have seronegative MG, without detectable antibodies against AChRs or MuSK, but still exhibit clinical symptoms and neurophysiologic findings of MG. This group poses a diagnostic challenge and often requires careful monitoring and management.

Congenital myasthenic syndromes

While MG is primarily an acquired autoimmune disorder, congenital myasthenic syndromes (CMS) represent a group of inherited neuromuscular disorders that can present similarly to MG but are due to genetic defects in the neuromuscu-

lar junction's components.[22] CMS have an estimated prevalence of 1–20 per 1000,000 individuals.[23] They are caused by genetic mutations affecting proteins essential for neuromuscular transmission at the neuromuscular junction. CMS is categorized based on the location of the defect: presynaptic, synaptic, and postsynaptic, with postsynaptic defects (such as mutations in the *CHRNE* gene) being the most common.[24] Pathologically, CMS leads to impaired communication between nerve and muscle, resulting in muscle weakness and fatigue that typically begins in infancy or childhood. Diagnosis often requires genetic testing and specialized electrophysiological studies. Treatment depends on the specific subtype and may include acetylcholinesterase inhibitors (e.g., pyridostigmine), beta-2 adrenergic agonists (e.g., albuterol or salbutamol), and 3,4-diaminopyridine, all aimed at enhancing neuromuscular transmission and improving muscle strength.[24] However, the response can differ significantly from that of autoimmune MG.

Diagnostic approaches in myasthenia gravis

Due to the variable presentation of symptoms, diagnosing MG can be challenging. A comprehensive approach that combines clinical assessment, serological testing, electrophysiological studies, and imaging is essential.

Clinical assessment

A thorough medical history is critical in the initial evaluation of suspected MG. Patients often report fluctuating weakness that worsens with activity and improves with rest. Specific symptoms such as ptosis, diplopia, dysphagia, or limb weakness should be documented. A history of autoimmune diseases in the family may suggest a genetic predisposition to MG. Certain factors such as infections, stress, and specific medications (e.g., muscle relaxants) can exacerbate symptoms and should be explored.

A neurological examination is crucial for identifying characteristic findings associated with MG. A detailed ocular exam evaluating for ptosis and diplopia is essential. These findings may fluctuate during the examination, particularly with fatigue. Assessing strength in various muscle groups, especially proximal muscles, can help identify patterns of weakness typical of MG. The "fatigability" aspect of muscle strength may be assessed through repetitive testing.

Serological testing

Serological tests are vital for confirming the diagnosis of MG and involve the detection of specific autoantibodies. Approximately 80 % of patients with generalized MG have antibodies against acetylcholine receptors (AChRs). The presence of these antibodies is a strong indicator of the disease.[13] The detection is typically performed using enzyme-linked immunosorbent assay (ELISA) or radioimmunoassay (RIA). The AChR antibody test has high sensitivity and specificity for generalized MG.[26] False positive AChR antibody test results may occur in clinical practice and associates with low antibody titers.[27] Failure to recognize false antibody positivity may lead to misdiagnosis and inappropriate treatments**.**

In patients who test negative for AChR antibodies, particularly those with more severe bulbar symptoms, testing for muscle-specific kinase (MuSK) antibodies is indicated. MuSK antibodies are found in about 5–10 % of MG cases.[26] While AChR and MuSK antibodies are the most tested, other autoantibodies such as those against low-density lipoprotein receptor-related protein 4 (LRP4) or agrin may also be assessed, particularly in seronegative cases.[26] The prevalence rates of LRP4 or agrin antibodies in seronegative cases are highly variable in the literature.[28] LRP4 and agrin antibody-positive patients are reported to have more severe clinical disease than antibody-negative patients.[29] However, most seronegative cases respond to standard therapy regardless of LRP4 or agrin antibody status.[29]

Electrophysiological studies

Electrophysiological tests are essential in evaluating neuromuscular transmission and confirming the diagnosis of MG. Repetitive Nerve Stimulation (RNS) involves stimulating a motor nerve multiple times and measuring the amplitude of the muscle electrical response. In MG, a decremental response is typically observed—meaning that the muscle response decreases with repeated stimulation. This finding is indicative of impaired neuromuscular transmission.[26]

Single-fiber electromyography is a more sensitive test that assesses the electrical activity of individual muscle fibers. Single-fiber electromyography measures "jitter," which refers to the variability in the time it takes for muscle fibers to respond to nerve stimulation. Increased jitter is highly suggestive of MG, even in patients who may have normal RNS results.[26] This test is often considered only when other diagnostic tests are unrevealing.

Imaging studies

The thymus gland plays a significant role in MG, with many patients exhibiting thymic abnormalities such as hyperplasia or thymomas. A chest computed tomography (CT) scan is necessary to evaluate for thymoma. Thymomas are associated with a higher incidence of MG and may require surgical intervention.[28,29]

Conclusions

Myasthenia gravis is a complex autoimmune disorder that requires a comprehensive approach to diagnosis and management. The pathophysiological mechanisms of myasthenia gravis are multifaceted, involving a complex interplay of autoantibodies, thymic abnormalities, complement activation, and immune cell interactions. Myasthenia gravis presents a spectrum of clinical syndromes, each with distinct features and challenges. Ocular symptoms often serve as an early indicator, while generalized weakness may progress to life-threatening conditions like myasthenic crisis. Awareness of congenital forms and variants further highlights the complexity of MG, emphasizing the need for tailored therapeutic approaches. The diagnosis of myasthenia gravis requires a methodical approach involving clinical assessment, serological testing, electrophysiological studies, and imaging. Early and accurate diagnosis, as well as personalized management strategies, including pharmacological interventions, thymectomy, and supportive therapies, can significantly enhance the quality of life for individuals living with MG and lead to improved patient outcomes. Ongoing research into the underlying pathophysiology and novel therapies holds promise for improved management of this challenging condition.

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